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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,522	11/21/2001	Choy-Pik Chiu	097/002	3556

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/990,522	CHIU ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 29 June 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ they raise the issue of new matter (see Note below);
   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____.
3. ☐ Applicant's reply has overcome the following rejection(s): _____.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-20*.

   Claim(s) withdrawn from consideration: _____.
8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____
10. ☐ Other: _____

DAVID GUZO
PRIMARY EXAMINER

Continuation of 5. does NOT place the application in condition for allowance because: Applicants' arguments are respectfully not found persuasive over the rejection of record.

1. With respect to Applicants' request for rejoinder of all species because no prior art has been identified to anticipate claim 1, please note that generic claims with the elected species (e.g., mesenchymal stem cells or first cell population expressing CD90 and cardiomyocytes as the second cell population) are still rejected under 35 USC 112 First Paragraph for the reasons of record. Therefore, there is no requirement for the examiner to examine and search for all other pending species. Furthermore, Applicants elected the aforementioned species without traverse in the amendment filed on 4/7/03.

2, With respect to Applicants' argument that the claims are rejected because the specification does not include a working example of the invention. Please note that lack of a working example is only one of several Wands factors for which the enablement rejection was based on, not solely because of the absence of a working example.

3. With respect to the issue whether effective populations of cardiomyocytes can be made from hPS cells, Applicants' arguments are based primarily on the Declaration under 37 CFR 1.132 from Dr. Joseph D. Gold, and that the patent disclosure does not have to provide every little detail that may be useful in putting an invention into practice.

It is noted that the method that is described by Dr. Gold in his Declaration for the preparation of cardiomyocytes from hES cells does not have the same method steps and starting materials as the described method of the present invention (see instant specification, page 11, lines 30-36 and the Declaration, page 2, third full paragraph), and therefore his disclosed results are not relevant. Furthermore, it is unclear whether his nude rat model is a representative or acceptable model for any individual (human included) in need of therapy.

On the contrary to Applicants' assertion that the instant disclosure fails to provide only little and non-critical details, and that the implementation of any laboratory method will involve some degree of optimization that would only require routine experiementation, Xu et al. (already cited in the Final Office Action) have stated "The difference in the efficiency of cardiomyocytes differentiation may reflect differences in culture conditions of the undifferentiated hES cells, methods used for the dissociation of hES cells to generate Ebs, the length of EB suspension culture and/or the quality of serum used for differentiation", indicating that these culture conditions are not little or non-critical details. Particularly, in light of the overall state of the prior art as already discussed in the Final Office Action.

4. With respect to the issue whether hPS derived mesenchymal cells are capable of inducing tolerance, Applicants submitted a second Declaration of Dr. Anish Majumdar showing the immortalized HEF1 cell line expressing exogenous hTERT and a CD29, CD44, CD71, CD90 and CD45 negative and CD14 negative phenotype is capable of inhibiting an immune reaction by third-party cells in a mixed lymphocyte reaction.

Once again, it is noted that the instant specification fails to provide the exact conditions that are used for the preparation of the HEF1 cell line disclosed in the second Declaration of DR. Anish Majumdar. Please note that the specification specifically teaches that "cobblestone-like appearance" colony was selected, passaged and monitored for phenotypic markers (page 13, lines 5-16), and not "fibroblastic" HEF1 cells, let alone that the cells are further transfected with a recombinant retrovirus expressing hTERT. Therefore, the results disclosed in the second Declaration of Dr. Majumdar are not relevant to the presently elected invention. Furthermore, there is no evidence indicating that the parental cell line of HEF1 would behave or share the same properties as those of HEF1 cells, let alone human mesenchymal stem cells having toleragenic properties.

5. With respect to the post-filing art of Kuhr et al., Applicants argue that the question of tolerance induction is not relevant to the enablement of claims 1-13, and that this invention helps to solve both the problem of mismatch of HLA antigens in allograft tissue and the mismatch of minor histocompatiblility antigens. Particularly, the first and second cell populations will be derived from the same hPS cell line.

Please note that enablement requires the specification to teach how to make and use the claimed invention, and that claim 1 recites specifically "whereupon administration of the first population to an individual renders the individual immunotolerant to the second cell population", and claim 8 recites "a first cell population that has been differentiated from human pluripotent stem (hPS) cells into a phenotype that renders a subject to whom it is administered immunotolerant to a second cell population", for examples.

The cited post-filing Kuhr article does not contradict in any way with the teachings of the Nobel laureates. Kuhr et al. clearly states that "In vitro assays of alloimmune response, such as mixed lymphocyte reaction (MLR), have not proven reliable for determining responsiveness between DLA-identical canines differing only in minor MHC antigens" (page 1491, col. 2, last line continues to line 3 of col. 1 on page 1492). If the assay is not reliable for determining alloimmune responses that are capable of rejecting allografts, then how is it reliable to extend the results obtained from mixed lyphocytes reactions in vitro to the therapeutic effects contemplated by Applicants (e.g., administration of the first cell population that has been differentiated from hPS cells into a phenotype that renders a subject to whom it is administered immunotolerant to a second cell population that is MHC compatible, that is not necessarily differentiated from the same hPS cell line)?

On the basis of the overall analysis of the Wands factors set forth in the Final Rejection mailed on 3/9/04, and for the reasons set forth in the precdeding paragraphs, claims 1-20 stand rejected under 35 USC 112, first paragraph.